



Elevated lipoprotein(a) and risk of coronary heart disease according to different lipid profiles in the general Chinese community population: the CHCN-BTH study

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Background: To evaluate the contributions of elevated lipoprotein(a) [Lp(a)] to the risk of coronary heart disease (CHD) in the general Chinese community population according to different lipid profiles.

Methods: We recruited individuals aged over 18 years from the baseline survey of the Cohort Study on Chronic Disease of Communities Natural Population in Beijing, Tianjin and Hebei (CHCN-BTH) using a stratified, multistage cluster sampling method. Data were collected through questionnaire surveys, anthropometric measures and laboratory tests. Restricted cubic spline (RCS) functions, multivariate logistic regression, sensitivity analyses and stratified analyses were used to evaluate the association between Lp(a) and CHD.

Results: A total of 25,343 participants were included, with 1,364 (5.38%) identified as having CHD. Elevated Lp(a) levels were linearly related to an increased risk of CHD ($P_{\text{overall-association}} < 0.0001$ and $P_{\text{nonlinear-association}} = 0.8468$). Multivariate logistic regression analysis indicated that subjects with Lp(a) ≥ 300 mg/L had a higher risk of CHD [OR (95% CI): 1.36 (1.17, 1.57)] than did individuals with Lp(a) < 300 mg/L. Compared with individuals with Lp(a) < 119.0 mg/L (< 50 th percentile), the ORs (95% CI) for CHD in the 51st–80th, 81st–95th and > 95 th percentiles were 1.07 (0.93, 1.23), 1.26 (1.07, 1.50) and 1.68 (1.30, 2.17), respectively (P for trend < 0.0001). This association was also found among the subgroup of subjects without dyslipidemia, including those with normal total cholesterol (TC) (< 6.2 mmol/L), triglycerides (TG) (< 2.3 mmol/L), high-density lipoprotein cholesterol (HDL-C) (≥ 1.0 mmol/L) and low-density lipoprotein cholesterol (LDL-C) (< 4.1 mmol/L). Elevated Lp(a) and dyslipidemia significantly contributed to a higher risk of CHD with synergistic effects. Stratified analyses showed that elevated Lp(a) concentrations were significantly associated with an increased risk of CHD in the subgroups of individuals who were noncurrent drinkers, overweight individuals, individuals with hypertension, individuals who engaged in moderate physical activity, those

without diabetes mellitus and individuals in Beijing and Tianjin.

Conclusions: Elevated Lp(a) concentrations were linearly associated with a higher risk of CHD in the general Chinese community population, especially in normolipidemic subjects. Both dyslipidemia and elevated Lp(a) independently or synergistically contributed to the risk of CHD. Our results suggest that more attention should be paid to the levels of Lp(a) in normolipidemic subjects, which may be an early predictor of CHD.

Keywords: Lipoprotein(a); coronary heart disease (CHD); lipid profiles; general Chinese community population

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Introduction

Coronary heart disease (CHD) was one of the leading causes of death globally in 2016 (1). With the aging of the population, the acceleration of urbanization and changes in lifestyle, the morbidity and mortality of CHD are on the rise in China, especially in rural areas (2). It is estimated that 11 million people suffer from CHD in China (3). Dyslipidemia is commonly considered a prominent risk factor for CHD in clinical practice (4). Generally, lowering low-density lipoprotein cholesterol (LDL-C) by treatment with a statin is the primary goal in the prevention and treatment of CHD, while other lipid parameters are recommended as secondary or supplementary targets (5). However, a few patients being treated with a statin still experience a substantial residual risk of events after the effective control of LDL-C to clinically normal levels (6). Therefore, the identification of the residual risk of biomarkers is of great importance for the prevention and treatment of CHD.

Studies have suggested that lipoprotein(a) [Lp(a)] may hold promise as a clinical marker to identify adults who are at risk of CHD (7,8). Lp(a) was first discovered by the Norwegian geneticist Berg in the northern European population in 1963 (9). It consists of an apolipoprotein B100 in a low-density lipoprotein (LDL)-like particle, covalently linked to a plasminogen-like glycoprotein apolipoprotein(a) [apo(a)] (10). Circulating Lp(a) levels are largely determined by the LPA gene locus and vary markedly across different ethnicities and regions (7,11,12).

Several studies have reported that elevated Lp(a) concentrations were associated with an increased risk of CHD (13-16). However, due to different assays of Lp(a), racial differences, heterogeneity and complexity of the structure of Lp(a), studies have reported inconsistent results (17). The Multi-Ethnic Study of Atherosclerosis

(MESA) (12) revealed no relation between Lp(a) and CHD in 548 Chinese-American individuals regardless of whether the 300 or 500 mg/L cutoff for Lp(a) was used after stratification by race/ethnicity. Studies have shown that the association between Lp(a) and CHD may be greatly attenuated by the level of LDL-C (18,19).

There are limited data regarding the association between Lp(a) and CHD in China. Previous studies found that elevated Lp(a) was an independent risk factor for coronary atherosclerotic heart disease (20), coronary artery disease (CAD) (21), cardiovascular events (22), myocardial infarction (23), and coronary artery calcification (24) in the Chinese Han population. However, the Chin-Shan Community Cardiovascular Cohort Study of 3484 community-based ethnic Chinese in Taiwan showed negative results with respect to the relationship between Lp(a) concentration and CHD with Lp(a) concentration cutoff values at the 90th, 95th, and 99th percentiles (25). Thus, associations between elevated Lp(a) and the risk of CHD need to be confirmed in a large-scale Chinese population. Moreover, the role of Lp(a) in subjects with well-controlled lipid levels remains unclear (26). Therefore, the aim of our study was to investigate the contributions of elevated Lp(a) to the risk of CHD and to explore the synergistic effect between Lp(a) and lipid profiles in a large-scale general Chinese community population.

We present the following article in accordance with the STROBE Statement reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3899>).

Methods

Study design and participants

All the data in this study were from participants enrolled in

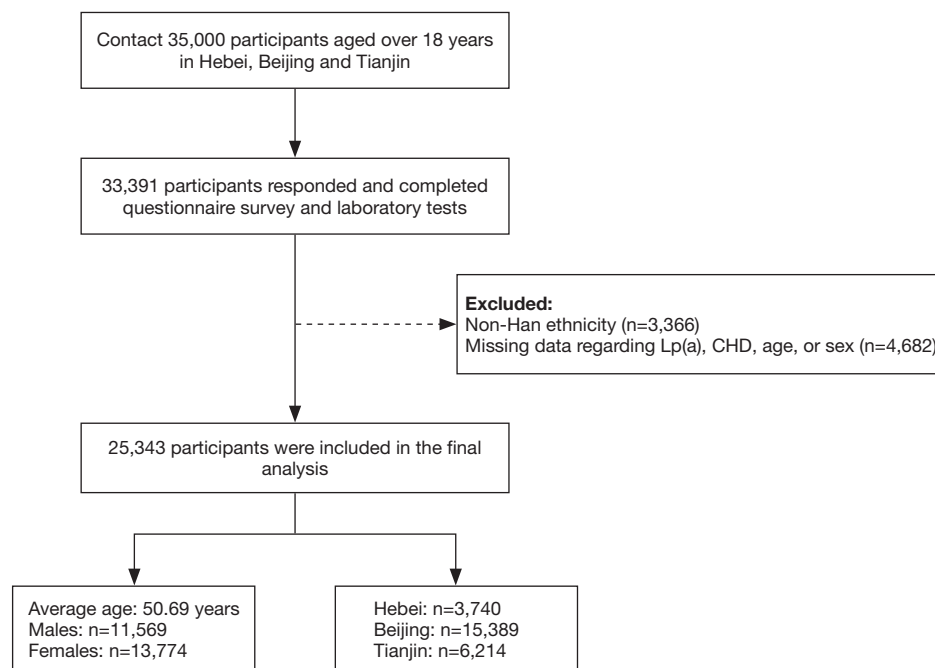


Figure 1 Flowchart for participant selection. CHD, coronary heart disease; Lp(a), lipoprotein(a).

the baseline survey titled “*Cohort Study on Chronic Disease of Communities Natural Population in the Beijing-Tianjin-Hebei Region*” (CHCN-BTH). The study was established with a multistage, stratified cluster sampling method in July 2017, with the aim of determining the associations between various risk factors and chronic diseases in community-based residents in the Beijing-Tianjin-Hebei region. The sampling process was stratified by geographical region, urbanization level and economic development status. The survey sites covered different economic areas, including the central core functional area, the area south of the expansion and the northwestern ecological conservation area. We selected districts from cities and rural townships from counties. Communities were selected from districts in urban areas, while villages were selected from townships in rural areas. Residents who had lived in the selected areas for at least 1 year and who were older than 18 years were all invited to participate in the survey.

A total of 33,391 participants responded and completed the questionnaire survey and laboratory tests. In this study, individuals were excluded if they were of non-Han ethnicity (n=3,366) or had missing data for CHD, Lp(a) and the key demographic variables (including age and sex) (n=4,682). Finally, 25,343 participants were included in the following analysis. The flowchart of participants is shown in *Figure 1*. A comparison of characteristics in the total cohort

population and included study participants was performed in *Table S1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Boards of Hebei Provincial Center for Disease Prevention and Control (No. IRB2017-003), Chaoyang District Center for Disease Prevention and Control (No. CYCDPCIRB-20170830-1) and Capital Medical University (No. 2018SY81), and informed consent was obtained from all the patients. This study was registered in the Chinese Clinical Trial Registry (ChiCTR). The trial registration number is ChiCTR1900024725 (<http://www.chictr.org.cn/showproj.aspx?proj=26656>).

Questionnaire survey

The participants completed the standard questionnaires during a face-to-face personal interview under the guidance of trained researchers. The questionnaire had three sections: (I) demographic and socioeconomic information (age, sex, race, education, marital status, occupation, monthly or annual income and family members); (II) health history and family history of hypertension, diabetes mellitus, CHD and other diseases, and medication use for hypertension and diabetes mellitus; and (III) lifestyle behaviors, including smoking, alcohol consumption and physical activity. All interviewers completed unified training before they

administered the formal survey. During the training session, we distributed detailed instructions regarding the administration of the questionnaire to the interviewers.

Anthropometric measurements and laboratory tests

All anthropometric measurements were performed by trained researchers following standard procedures. Height was measured to the nearest 0.1 cm using a standard stadiometer. Weight was measured to the nearest 0.1 kg by a body composition analyzer (TANITA BC-420, Japan). Participants were required to take off their coats and wear light clothing during the measurements of height and weight. We took three measurements of each participant's blood pressure and heart rate with a digital sphygmomanometer (Omron HEM-907, Japan). Before the measurements, all subjects were required to quietly rest for at least 5 minutes, avoiding strenuous exercise, eating, smoking, and drinking tea or caffeinated beverages for at least 30 minutes before the measurement. Subjects were asked to not speak during the measurement.

Blood samples were collected in the early morning, with all subjects having fasted for at least 8 hours prior to testing. Serum and plasma samples were isolated and immediately frozen at -20°C . All isolated samples were shipped on dry ice to the laboratory of Capital Medical University and frozen at -80°C after the site investigation. To improve the precision of the measurements, all blood biochemical tests were performed using the Beckman Coulter chemistry analyzer AU5800 in the clinical laboratory of Beijing Hepingli Hospital, and all testing personnel were blinded to the study data. Concentrations of total cholesterol (TC) and triglycerides (TG) were determined enzymatically using the cholesterol oxidase method and GPO-POD method, respectively. High-density lipoprotein cholesterol (HDL-C) levels were tested by the chemical modification enzyme method. LDL-C levels were measured via the selective solubility method. The level of high-sensitivity C-reactive protein (hsCRP) was measured via the immunoturbidimetric method.

Measurement of lipoprotein(a) concentrations

The level of serum Lp(a) [total mass (mg/L)] was assayed with latex enhanced immunoturbidimetric diagnostic reagent kits (Sekisui Diagnostic Ltd) with apo(a) isoform-insensitive properties and a normal reference value less than 300 mg/L (27). This assay has a high sensitivity and

a linear range from 1 to 1,000 mg/L, using 3 independent calibrators and 2 quality control materials to control for apo(a) size heterogeneity. Measurements were conducted according to the instructions of the test kits. The intra-assay and inter-assay coefficients of variation of the Lp(a) tests were no more than 5% and 10%, respectively.

Definition of variables

Current smokers were defined as those who had smoked at least one cigarette per day in the past 6 months. Current drinkers were defined as those who had consumed at least 30 g of alcohol per week in the past 6 months. Physical activity was classified as low, moderate or vigorous according to the intensity (28). Body mass index (BMI) was calculated as the body mass (kg) divided by the square of the body height (m^2) and was grouped according to the parameters established by the Department of Disease Control Ministry of Health in China: normal weight (BMI $<24.0\text{ kg/m}^2$), overweight (BMI 24.0 to $<28.0\text{ kg/m}^2$) and obesity (BMI $\geq 28.0\text{ kg/m}^2$) (29).

The information on medical history was self-reported by participants. Participants were considered to have CHD if they answered “yes” to the following question: “*Have you ever been told by a physician or a health care professional that you have coronary heart disease/diseases of heart vessels?*” Participants were specifically asked about the diagnosis of “myocardial infarction, angina pectoris, myocardial ischemia, heart stent implantation or coronary artery bypass graft surgery” if they answered “yes” to the original question (30). Previous studies have confirmed the accuracy of this approach for epidemiological assessments (31,32). Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg or the current use of anti-hypertensive medications (33). Diabetes mellitus was defined as a fasting serum glucose level ≥ 7.0 mmol/L or the current use of insulin or hypoglycemic drugs (34). Dyslipidemia was defined according to the criteria of the 2016 Chinese guidelines for the management of dyslipidemia in adults (35). Dyslipidemia was defined as any of the following abnormal blood lipid measurements: self-reported hypercholesterolemia; TC ≥ 6.2 mmol/L; TG ≥ 2.3 mmol/L; LDL-C ≥ 4.1 mmol/L; and HDL-C ≤ 1.0 mmol/L. The level of hsCRP ≥ 2 mg/L was defined as elevated (5). Levels of Lp(a) ≥ 300 mg/L were classified as elevated (35).

Statistical analysis

The baseline characteristics for continuous variables are

described as the means \pm standard deviations or medians (interquartile range, IQRs). The continuous variables were compared using Student's *t*-test, generalized linear model (GLM), the Kruskal-Wallis test, or the Wilcoxon rank-sum test, depending on the normality of the data and the groups. The frequencies for categorical variables were compared using the χ^2 test or the Cochran-Mantel-Haenszel test. P values for trend were derived from the Cochran-Armitage trend test. Bonferroni correction was performed for multiple comparison testing. Missing data (1, 2, 778, 778, 839 and 839 participants for TG, hsCRP, SBP, DBP, height and weight, respectively) were addressed through the mean or median imputation method. Pearson correlation and Spearman's test were performed to explore the correlation between Lp(a) and lipid profiles. Restricted cubic spline (RCS) functions were used to examine the dose-response association between Lp(a) and CHD with 3 knots (at the 50th, 80th and 95th percentiles) according to the best fit (36).

Participants were categorized into four groups according to predetermined percentiles of Lp(a), which best reflected the higher risk usually seen for individuals with extremely high Lp(a) levels (37). The percentiles chosen and the corresponding Lp(a) levels were <50th (<119.0 mg/L), 51st to 80th (119.0–281.2 mg/L), 81st to 95th (281.2–607.9 mg/L), and >95th (>607.9 mg/L). Univariate and multivariable unconditional logistic regression models were used to evaluate the association between Lp(a) concentrations and the risk of CHD in the total population and subgroups with different lipid profiles after adjustments for confounding factors (region, age, sex, BMI, TG, HDL-C, LDL-C, hsCRP, current smokers, current drinkers, family history of CHD, physical activity, hypertension, and diabetes mellitus). We also created dummy variables for the multicategory variables [Lp(a) percentiles, region and physical activity] and used them in our models. SAS Proc CATMOD analysis was used to assess homogeneity for $k \times R \times C$ tables, which was set up by fitting a log-linear model and testing the fit with the three-way interaction removed. Receiver operating characteristic (ROC) curve analysis was conducted to calculate the area under the curve (AUC), sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) to identify the optimal cutoff value of Lp(a) for the diagnosis of CHD. To validate the findings regarding elevated plasma Lp(a) levels, sensitivity analyses were conducted in subjects with any three normal blood lipid indexes (TC, TG, HDL-C, LDL-C).

Finally, stratified analyses were performed for elevated

Lp(a) concentrations and the risk of CHD according to baseline characteristics, including age (<65, \geq 65 years), sex, current smokers (yes or no), current drinkers (yes or no), hypertension (with or without), diabetes mellitus (with or without), region (Hebei Province, Beijing, Tianjin), BMI (normal, overweight, obesity) and physical activity (low, moderate, vigorous). All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium). Statistical tests were two-tailed, and P value <0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 25,343 eligible participants, comprising 11,569 (45.65%) males and 13,774 (54.35%) females, were included in the final analysis. The mean age of the study population was 50.69 ± 14.44 years old. The prevalence rate of CHD was 5.38%, with 1,364 participants identified as having CHD. For all the subjects, the distribution of Lp(a) levels was positively skewed with a median of 119.0 mg/L (59.0–236.7 mg/L, [Figure S1](#)). The percentiles and corresponding levels of Lp(a) in the total population are shown in [Table S2](#).

The characteristics of the study population are summarized in [Table 1](#). A decreasing trend was observed in the proportion of males, BMI, SBP, DBP, TG, HDL-C, region, proportions of current smokers/drinkers, prevalence of hypertension and prevalence of diabetes mellitus with increasing Lp(a) levels, by trend test ($P < 0.05$). However, an increasing trend was observed in age, fasting glucose, hsCRP, TC, LDL-C, prevalence of a family history of CHD and prevalence of CHD with increasing Lp(a) levels ($P < 0.05$). Compared with those with normal Lp(a) levels (<300 mg/L), the group of subjects with elevated Lp(a) levels (≥ 300 mg/L) had the following characteristics: older age; lower BMI SBP, DBP; higher fasting glucose and proportions of participants with abnormal TC and LDL-C; lower proportions of participants with abnormal TG and HDL-C; lower proportions of males, current smokers/drinkers, those engaging in vigorous physical activity, those with hypertension and those with diabetes mellitus; and more participants with CHD ([Table S3](#), all P values <0.05). There was no statistical significance for the levels of hsCRP and proportion of participants with a family history of CHD between the two groups ($P > 0.05$). Both dichotomous Lp(a)

Table 1 Characteristics of the total population according to lipoprotein(a) percentiles

Variables	Total	Lp (a) percentiles (mg/L)				P
		<50th (<119.0)	51st–80th (119.0–281.2)	81st–95th (281.2–607.9)	>95th (>607.9)	
Age (years)	50.69±14.44	50.43±14.12	50.87±14.63	50.76±14.87	51.89±15.05*	0.0026
Sex [male, (n, %)]	11,569 (45.65)	5,936 (46.88)	3,453 (45.38)	1,696 (44.60)	484 (38.17)*#&	<0.0001 [‡]
BMI (kg/m ²)	25.33±3.57	25.55±3.63	25.19±3.54*	25.06±3.46*	24.80±3.36*#	<0.0001
SBP (mmHg)	130.23±19.06	131.19±19.00	129.68±19.20*	128.52±18.66*	129.05±19.38*	<0.0001
DBP (mmHg)	77.58±11.70	78.28±11.74	77.15±11.66*	76.53±11.55*	76.32±11.57*	<0.0001
Fasting glucose (mmol/L)	5.46 (5.04,6.00)	5.40 (5.00,6.00)	5.50 (5.10,6.00)	5.50 (5.10,6.00)	5.50 (5.20,6.00)	<0.0001
hsCRP (mg/L)	1.06 (0.53,2.17)	1.05 (0.51,2.11)	1.08 (0.54,2.26)*	1.06 (0.55,2.17)	1.06 (0.54,2.29)	0.0486
Lp (a) (mg/L)	119.0 (59.0,236.7)	59.0 (35.9, 85.9)	176.3 (144.1,219.3)	382.3 (324.8,465.6)	786.1 (682.0,956.1)	<0.0001
TC ≥6.2 mmol/L	3,636 (14.35)	1,473 (11.63)	1,187 (15.60)*	688 (18.09)*#	288 (22.71)*#&	<0.0001 [‡]
TG ≥2.3 mmol/L	4,312 (17.01)	2,612 (20.63)	1,051 (13.81)*	482 (12.67)*	167 (13.17)*	<0.0001 [‡]
HDL-C <1.0 mmol/L	3,465 (13.67)	2,101 (16.59)	872 (11.46)*	385 (10.12)*	107 (8.44)*#	<0.0001 [‡]
LDL-C ≥4.1 mmol/L	2,672 (10.54)	1,013 (8.00)	927 (12.18)*	503 (13.23)*	229 (18.06)*#&	<0.0001 [‡]
Region (n, %)						<0.0001 [‡]
Hebei	3,740 (14.76)	2,228 (17.59)	944 (12.41)	455 (11.96)	113 (8.91)	
Beijing	15,389 (60.72)	6,791 (53.63)	4,974 (65.37)	2,614 (68.74)	1,010 (79.65)	
Tianjin	6,214 (24.52)	3,644 (28.78)	1,691 (22.22)	734 (19.30)	145 (11.44)	
Current smokers (n, %)	7,870 (31.05)	4,144 (32.73)	2,326 (30.57)*	1,093 (28.74)*	307 (24.21)*#&	<0.0001 [‡]
Current drinkers (n, %)	10,145 (40.03)	5,221 (41.23)	3,020 (39.69)	1,457 (38.31)*	447 (35.25)*#	<0.0001 [‡]
Physical activity (n, %)						0.0023 [‡]
Low	3,850 (15.19)	2,023 (15.98)	1,126 (14.80)	553 (14.54)	148 (11.67)	
Moderate	16,559 (65.34)	8,227 (64.97)	4,931 (64.80)	2,533 (66.61)	868 (68.45)	
Vigorous	4,934 (19.47)	2,413 (19.06)	1,552 (20.40)	717 (18.85)	252 (19.87)	
Family history of CHD (n, %)	4,854 (19.15)	2,324 (18.35)	1,493 (19.62)	765 (20.12) [#]	272 (21.45)*	0.0004 [‡]
CHD (n, %)	1,364 (5.38)	663 (5.24)	395 (5.19)	219 (5.76)	87 (6.86)	0.0273 [‡]
Hypertension (n, %)	10,431 (41.16)	5,403 (42.67)	3,069 (40.33)*	1,469 (38.63)*	490 (38.64)*	<0.0001 [‡]
Diabetes mellitus (n, %)	3,711 (14.64)	1,979 (15.63)	1,053 (13.84)*	499 (13.12)*	180 (14.20)	0.0001 [‡]

[†], Cochran-Mantel-Haenszel test. [‡], Cochran-Armitage trend test. *, P<0.05/6=0.0083 compared with Lp (a) (<50th). [#], P<0.05/6=0.0083 compared with Lp (a) (51st–80th). [&], P<0.05/6=0.0083 compared with Lp (a) (81st–95th). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; Lp (a), lipoprotein (a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease.

and Lp(a) percentiles were significantly different among all lipid profiles (P<0.05) except dyslipidemia (P=0.1724, P=0.7622, [Tables S4,S5](#)). The proportion of elevated Lp(a) levels increased with the increasing severity of dyslipidemia (P<0.05).

Correlation analysis for lipoprotein(a) and lipid profiles

The correlation analysis for Lp(a) and lipid profiles is shown in [Table 2](#). Lp(a) was positively correlated with TC, HDL-C and LDL-C and negatively correlated with TG (P<0.05).

Table 2 Correlation analysis for lipoprotein(a) and lipid profiles in the total population

Variables	Lp(a)	TC	TG	HDL-C	LDL-C
Lp(a) [†]	1.000				
TC	0.140	1.000			
TG [†]	-0.088	0.292	1.000		
HDL-C	0.111	0.195	-0.512	1.000	
LDL-C	0.175	0.900	0.302	NS	1.000

[†], for variables that were not normally distributed, Spearman's test was performed. Otherwise, Pearson's correlation was performed. All the P values for correlations were significant (<0.05) except that denoted NS (not significant). Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

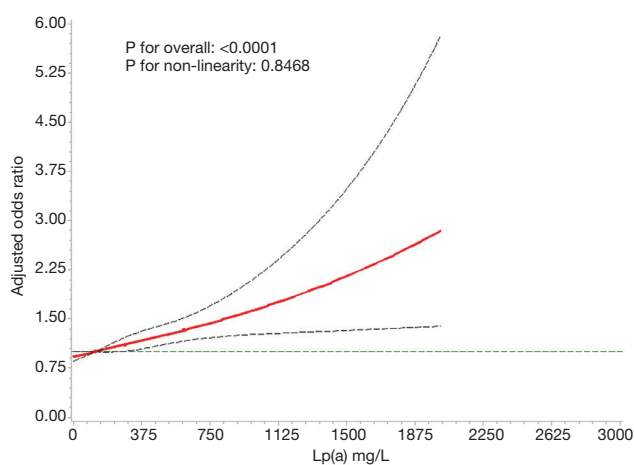


Figure 2 The dose-response association between elevated lipoprotein(a) levels and the risk of coronary heart disease using restricted cubic spline functions with 3 knots (50th, 80th, 95th) in the total population. The x-axis indicates the level of Lp(a) (mg/L). The y-axis represents the OR for CHD for any value of Lp(a) compared to individuals with the median level of Lp(a) (119.0 mg/L). Dashed lines are the 95% CIs of the ORs. Knots are represented by dots. The model was adjusted for region, age, sex, BMI, TG, HDL-C, LDL-C, hsCRP, current smokers, current drinkers, physical activity, family history of CHD, hypertension, and diabetes mellitus. Abbreviations: CHD, coronary heart disease; Lp(a), lipoprotein(a); BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

Dose-response relationship analysis for elevated lipoprotein(a) levels and risk of CHD

The RCS analysis indicated that there was a linear dose-response association between Lp(a) and CHD with 3 knots (50th, 80th, 95th) after multivariable adjustment in the total population (*Figure 2*, P for overall association test <0.0001 and P for nonlinear association test =0.8468). The ORs (95% CIs) for the 80th (281.2 mg/L) and 95th (607.9 mg/L) Lp(a) percentiles were 1.11 (1.01, 1.22) and 1.33 (1.17, 1.52), respectively, compared with the reference 50th percentile (119.0 mg/L).

Association between lipoprotein(a) concentrations and the risk of CHD in the total population and subgroups with different lipid profiles

Compared with individuals with Lp(a) <300 mg/L, individuals with Lp(a) ≥300 mg/L had a multivariable-adjusted OR (95% CI) for CHD of 1.36 (1.17, 1.57) after adjustments for confounding factors (*Table S6*). The same association was also found among the subgroups of normolipidemic subjects [1.41 (1.12, 1.77)], those with dyslipidemia [1.24 (1.02, 1.50)], those with TC <6.2 mmol/L [1.38 (1.17, 1.62)], those with TG <2.3 mmol/L [1.39 (1.18, 1.63)], those with HDL-C ≥1.0 mmol/L [1.38 (1.18, 1.62)] and those with LDL-C <4.1 mmol/L [1.35 (1.15, 1.59)].

Compared with individuals with Lp(a) <119.0 mg/L (<50th percentile), the multivariable-adjusted OR (95% CI) for CHD was 1.07 (0.93, 1.23) for individuals with Lp(a) levels of 119.0 to 281.2 mg/L (51st–80th percentiles), 1.26 (1.07, 1.50) for individuals with Lp(a) levels of 281.2 to 607.9 mg/L (81st–95th percentiles) and 1.68 (1.30, 2.17) for individuals with Lp(a) >607.9 mg/L (>95th percentile) in the total population (*Table 3*). The same association was also detected among the subgroup of normolipidemic subjects [2.09 (1.41, 3.08)], those with TC <6.2 mmol/L [1.94 (1.47, 2.56)], those with TG <2.3 mmol/L [1.71 (1.30, 2.25)], those with HDL-C ≥1.0 mmol/L [1.74 (1.33, 2.28)] and those with LDL-C <4.1 mmol/L [1.90 (1.44, 2.50)]. There was no heterogeneity in the associations between Lp(a) and the risk of CHD among the subgroups with other profiles (all P values >0.05). The P values for stratified variables, including dyslipidemia, TC, TG, HDL-C and LDL-C, were 0.7296, 0.1073, 0.6798, 0.5796 and 0.1141, respectively.

Table 3 Odds ratios of coronary heart disease by lipoprotein(a) percentiles according to different lipid profiles

Population	Lp(a) percentiles (mg/L)				P for trend
	<50th (<119.0)	51st–80th (119.0–281.2)	81st–95th (281.2–607.9)	>95th (>607.9)	
Total					
N of CHD (%)	663 (5.24)	395 (5.19)	219 (5.76)	87 (6.86)	0.0273 [‡]
Unadjusted	1	0.99 (0.87,1.13)	1.11 (0.95,1.29)	1.33 (1.06,1.68)	0.0274
Adjusted [†]	1	1.07 (0.93,1.23)	1.26 (1.07,1.50)	1.68 (1.30,2.17)	<0.0001
Normolipidemia					
N of CHD (%)	264 (3.61)	166 (3.61)	90 (3.99)	37 (5.36)	0.0605 [‡]
Unadjusted	1	1.00 (0.82,1.22)	1.11 (0.87,1.42)	1.52 (1.06,2.16)	0.0606
Adjusted [†]	1	1.06 (0.85,1.31)	1.24 (0.95,1.62)	2.09 (1.41,3.08)	0.0015
Dyslipidemia					
N of CHD (%)	399 (7.47)	229 (7.61)	129 (8.34)	50 (8.65)	0.1778 [‡]
Unadjusted	1	1.02 (0.86,1.21)	1.13 (0.92,1.39)	1.17 (0.86,1.60)	0.1779
Adjusted [†]	1	1.04 (0.87,1.24)	1.20 (0.96,1.49)	1.29 (0.93,1.80)	0.0524
TC <6.2 mmol/L					
N of CHD (%)	578 (5.17)	330 (5.14)	175 (5.62)	75 (7.65)	0.0112 [‡]
Unadjusted	1	1.00 (0.87,1.14)	1.09 (0.92,1.30)	1.52 (1.19,1.95)	0.0113
Adjusted [†]	1	1.08 (0.93,1.26)	1.23 (1.02,1.49)	1.94 (1.47,2.56)	<0.0001
TC ≥6.2 mmol/L					
N of CHD (%)	85 (5.77)	65 (5.48)	44 (6.40)	12 (4.17)	0.6977 [‡]
Unadjusted	1	0.95 (0.68,1.32)	1.12 (0.77,1.63)	0.71 (0.38,1.32)	0.6977
Adjusted [†]	1	1.05 (0.74,1.50)	1.50 (1.00,2.25)	0.93 (0.48,1.79)	0.2928
TG <2.3 mmol/L					
N of CHD (%)	506 (5.03)	324 (4.94)	185 (5.57)	76 (6.90)	0.0219 [‡]
Unadjusted	1	0.98 (0.85,1.13)	1.11 (0.94,1.32)	1.40 (1.09,1.80)	0.0220
Adjusted [†]	1	1.04 (0.89,1.21)	1.25 (1.04,1.51)	1.71 (1.30,2.25)	0.0002
TG ≥2.3 mmol/L					
N of CHD (%)	157 (6.01)	71 (6.76)	34 (7.05)	11 (6.59)	0.3418 [‡]
Unadjusted	1	1.13 (0.85,1.51)	1.19 (0.81,1.74)	1.10 (0.59,2.08)	0.3421
Adjusted [†]	1	1.23 (0.90,1.68)	1.34 (0.88,2.02)	1.45 (0.74,2.86)	0.0711
HDL-C ≥1.0 mmol/L					
N of CHD (%)	522 (4.94)	345 (5.12)	193 (5.65)	80 (6.89)	0.0052 [‡]
Unadjusted	1	1.04 (0.90,1.19)	1.15 (0.97,1.36)	1.42 (1.12,1.82)	0.0053
Adjusted [†]	1	1.08 (0.93,1.26)	1.27 (1.05,1.52)	1.74 (1.33,2.28)	<0.0001

Table 3 (continued)

Table 3 (continued)

Population	Lp(a) percentiles (mg/L)				P for trend
	<50 th (<119.0)	51 st –80 th (119.0–281.2)	81 st –95 th (281.2–607.9)	>95 th (>607.9)	
HDL-C <1.0 mmol/L					
N of CHD (%)	141 (6.71)	50 (5.73)	26 (6.75)	7 (6.54)	0.7388 [†]
Unadjusted	1	0.85 (0.61,1.18)	1.01 (0.65,1.55)	0.97 (0.44,2.13)	0.7388
Adjusted [†]	1	1.03 (0.72,1.48)	1.23 (0.76,1.98)	1.27 (0.54,2.99)	0.3779
LDL-C <4.1 mmol/L					
N of CHD (%)	594 (5.10)	345 (5.16)	183 (5.55)	76 (7.31)	0.0140 [†]
Unadjusted	1	1.01 (0.88,1.16)	1.09 (0.92,1.30)	1.47 (1.15,1.88)	0.0141
Adjusted [†]	1	1.08 (0.94,1.26)	1.24 (1.03,1.49)	1.90 (1.45,2.50)	<0.0001
LDL-C ≥4.1 mmol/L					
N of CHD (%)	69 (6.81)	50 (5.39)	36 (7.16)	11 (4.80)	0.5139 [†]
Unadjusted	1	0.78 (0.54,1.14)	1.06 (0.69,1.60)	0.69 (0.36,1.33)	0.5140
Adjusted [†]	1	0.97 (0.65,1.45)	1.44 (0.91,2.27)	0.90 (0.45,1.81)	0.4764

[†], adjusted for region, age, sex, BMI, TG, HDL-C, LDL-C, hsCRP, current smokers, current drinkers, physical activity, family history of CHD, hypertension and diabetes mellitus. [‡], Cochran-Armitage trend test. Abbreviations: Lp(a), lipoprotein(a); CHD, coronary heart disease; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein.

Synergistic effects of lipoprotein(a) and lipid profiles on the risk of CHD

Elevated Lp(a) and dyslipidemia significantly contributed to a higher risk of CHD with synergistic effects. The OR (95% CI) for those with elevated Lp(a) (≥300 mg/L) and dyslipidemia was 1.71 (1.40, 2.09), when compared to those with Lp(a) <300 mg/L and normolipidemia (Table 4). Similarly, the OR (95% CI) for those with the highest Lp(a) levels (>95th) and dyslipidemia was 1.81 (1.29, 2.54), when compared to those with Lp(a) levels (<50th) and normolipidemia (Table S7). Synergistic effects were not found between Lp(a) and TC, TG, HDL-C or LDL-C with regard to the risk of CHD. Sensitivity analyses indicated that abnormal Lp(a) and TG collectively contributed to an increased risk of CHD among the population with normal TC, HDL-C and LDL-C levels (data not shown).

ROC curve analysis for lipoprotein(a) and CHD

In the multivariate ROC curve analysis, the AUC for Lp(a) was almost equal to those for other lipid profiles (Table 5). The sensitivity and specificity of Lp(a) were

84.1% (82.0, 86.0) and 69.3% (68.7, 69.9), respectively. The optimal cutoff value of Lp(a) for the diagnosis of CHD was 295.0 mg/L.

Stratified analyses for lipoprotein(a) and risk of CHD

We also conducted a stratified analysis for elevated Lp(a) concentrations and the risk of CHD according to baseline characteristics (Figure 3). Elevated Lp(a) concentrations were significantly associated with an increased risk of CHD in the following subgroups: noncurrent drinkers [OR (95% CI): 1.75 (1.28, 2.38)], those with hypertension [OR (95% CI): 1.74 (1.29, 2.36)], those without diabetes mellitus [OR (95% CI): 1.77 (1.31, 2.39)], individuals in Beijing [OR (95% CI): 1.81 (1.31, 2.51)] and individuals in Tianjin [OR (95% CI): 1.64 (1.00, 2.69)], those whose BMI was classified as overweight (24.0 ≤ BMI <28.0 kg/m²) [OR (95% CI): 1.82 (1.30, 2.55)], and those who engaged in moderate physical activity [OR (95% CI): 1.80 (1.33, 2.42)]. There was no heterogeneity in the associations between Lp(a) and the risk of CHD among the other subgroups (all P values >0.05). The P values for stratified variables, including age, sex, current smokers, current drinkers, hypertension, diabetes

Table 4 Odds ratios of coronary heart disease by dichotomous lipoprotein(a) according to different lipid profiles

Lipid profile and Lp(a) status	CHD (n, %)	OR (95% CI)
Dyslipidemia & Lp(a)		
Dyslipidemia (-) & Lp(a) (-)	440 (3.61)	1.00
Dyslipidemia (-) & Lp(a) (+)	117 (4.39)	1.42 (1.13, 1.77)
Dyslipidemia (+) & Lp(a) (-)	639 (7.49)	1.39 (1.21, 1.59)
Dyslipidemia (+) & Lp(a) (+)	168 (8.62)	1.71 (1.40, 2.09)
TC & Lp(a)		
TC (-) & Lp(a) (-)	926 (5.15)	1.00
TC (-) & Lp(a) (+)	232 (6.24)	1.38 (1.18, 1.63)
TC (+) & Lp(a) (-)	153 (5.59)	0.72 (0.55, 0.92)
TC (+) & Lp(a) (+)	53 (5.90)	0.92 (0.64, 1.32)
TG & Lp(a)		
TG (-) & Lp(a) (-)	847 (4.98)	1.00
TG (-) & Lp(a) (+)	244 (6.07)	1.37 (1.17, 1.61)
TG (+) & Lp(a) (-)	232 (6.25)	1.04 (0.88, 1.23)
TG (+) & Lp(a) (+)	41 (6.84)	1.36 (0.96, 1.93)
HDL-C & Lp(a)		
HDL-C (-) & Lp(a) (-)	883 (4.99)	1.00
HDL-C (-) & Lp(a) (+)	257 (6.15)	1.39 (1.19, 1.62)
HDL-C (+) & Lp(a) (-)	196 (6.48)	1.24 (1.03, 1.49)
HDL-C (+) & Lp(a) (+)	28 (6.38)	1.43 (0.94, 2.19)
LDL-C & Lp(a)		
LDL-C (-) & Lp(a) (-)	960 (5.13)	1.00
LDL-C (-) & Lp(a) (+)	238 (6.04)	1.36 (1.16, 1.60)
LDL-C (+) & Lp(a) (-)	119 (5.96)	0.75 (0.61, 0.93)
LDL-C (+) & Lp(a) (+)	47 (6.96)	1.01 (0.73, 1.40)

Dyslipidemia (-): without dyslipidemia; Dyslipidemia (+): with dyslipidemia. TC (-): TC <6.2 mmol/L; TC (+): TC ≥6.2 mmol/L. TG (-): TG <2.3 mmol/L; TG (+): TG ≥2.3 mmol/L. HDL-C (-): HDL-C ≥1.0 mmol/L; HDL-C (+): HDL-C <1.0 mmol/L. LDL-C (-): LDL-C <4.1 mmol/L; LDL-C (+): LDL-C ≥4.1 mmol/L. Lp(a) (-): Lp(a) <300 mg/L; Lp(a) (+): Lp(a) ≥300 mg/L. CHD, coronary heart disease; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

mellitus, region, BMI, and physical activity were 0.6871, 0.3234, 0.7149, 0.6587, 0.3289, 0.6141, 0.5188, 0.5317 and 0.4471, respectively.

Discussion

In this study, we found that higher Lp(a) levels were linearly related to an increased risk of CHD after adjustment for confounding factors. Subjects with Lp(a) ≥300 mg/L had a higher risk of CHD [OR (95% CI): 1.36 (1.17, 1.57)] than those with Lp(a) <300 mg/L. Compared with individuals with Lp(a) <119.0 mg/L (<50th percentile), those with Lp(a) >281.2 mg/L (81st–95th and >95th percentile) had a higher risk of CHD, especially in the subgroups of normolipidemic subjects, noncurrent drinkers, individuals with moderate physical activity, overweight individuals, those with hypertension and those without diabetes mellitus. In addition, we detected significant synergistic effects of elevated Lp(a) and dyslipidemia, which contributed to a higher risk of CHD. Subjects with elevated Lp(a) and dyslipidemia had a higher risk of CHD than those with normal Lp(a) levels and normolipidemia [OR (95% CI): 1.71 (1.40, 2.09) for Lp(a) ≥300 mg/L and dyslipidemia; OR (95% CI): 1.81 (1.29, 2.54) for Lp(a) >607.9 mg/L (>95th) and dyslipidemia].

Several large-scale studies have explored the relationship between Lp(a) levels and the risk of CHD and have reported similar findings (15,16,38). The Ludwigshafen Risk and Cardiovascular Health (LURIC) study from Germany reported that an increased severity of CHD was associated with Lp(a) concentrations in the highest tertile [adjusted HR (95% CI): 1.44 (1.14, 1.83)] (39). A study from the UK found that individuals in the top fifth in terms of Lp(a) levels had more than a twofold higher risk of CHD than those in the bottom fifth, and this association was independent of kringle IV type 2 (KIV 2) repeats [OR (95% CI): 2.05 (1.38, 3.04)] (13). The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study demonstrated that increased baseline Lp(a) concentrations were independently associated with an increased risk of total CHD events, total cardiovascular disease (CVD) events, and coronary events (40). Although the pathophysiology of Lp(a) remains unclear, studies have suggested that Lp(a) plays roles via three main potential mechanisms: the proatherogenic action of its LDL-like moiety, the thrombogenic and antifibrinolytic effects of its apo(a) moiety, and the proinflammatory effects of its oxidized phospholipid content (8). The studies above demonstrated that it was essential to measure Lp(a) for risk assessment and stratification among patients with known CHD.

Due to the lack of standardization and heterogeneity of

Table 5 Receiver operating characteristic curve analysis for lipoprotein(a) and lipid profiles for the diagnosis of coronary heart disease

Model [†]	AUC (95% CI)	Sensitivity (%)	Specificity (%)	+LR	-LR	Youden index	P
TC	0.842	86.4 (84.5, 88.2)	68.1 (67.5, 68.7)	2.7 (2.6, 2.8)	0.2 (0.2, 0.2)	0.5450	<0.0001
TG	0.837	86.6 (84.7, 88.3)	66.7 (66.1, 67.3)	2.6 (2.5, 2.7)	0.2 (0.2, 0.2)	0.5326	<0.0001
HDL-C	0.837	85.9 (84.0, 87.7)	67.7 (67.1, 68.3)	2.7 (2.6, 2.7)	0.2 (0.2, 0.2)	0.5361	<0.0001
LDL-C	0.841	85.2 (83.2, 87.0)	69.0 (68.4, 69.5)	2.7 (2.7, 2.8)	0.2 (0.2, 0.2)	0.5416	<0.0001
Lp(a)	0.837	84.1 (82.0, 86.0)	69.3 (68.7, 69.9)	2.7 (2.7, 2.8)	0.2 (0.2, 0.3)	0.5342	<0.0001

[†], adjusted for age, sex, BMI, hsCRP, current smokers, current drinkers, family history of CHD, physical activity, hypertension and diabetes mellitus. AUC, area under the curve; +LR, positive likelihood ratio; -LR, negative likelihood ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; CHD, coronary heart disease.

the available data, there is no universal clinical cutoff value for Lp(a) that identifies an increased risk of CVD (41). The European Atherosclerosis Society (EAS) (42) proposed 500 mg/L as the optimal level for Lp(a), which would mean that 20% of the population would have high concentrations. Nordestgaard *et al.* recommended 500 mg/L as the level to use to screen for elevated Lp(a) in those at intermediate or high risk of CVD (43). The 2016 guidelines for the management of dyslipidemia in adults in Canada (44) and China (35) considered 300 mg/L to be the cutoff for an elevated Lp(a) level. Similar to the proposal of the EAS (42), we found that individuals with Lp(a) >281.2 mg/L (in the top 20% of the population) had a higher risk of CHD. The optimal cutoff value of Lp(a) for the diagnosis of CHD was 295.0 mg/L. Both Lp(a) levels were lower than the cutoff point of 300 mg/L in China. The sensitivity and specificity of Lp(a) were roughly the same as those of other lipid indexes. The MESA study showed that Chinese individuals had a lower Lp(a) concentration (median =78 mg/L) than Africans, Arabs, Europeans, Latin Americans, South Asians, and Southeast Asians (11). A cross-sectional study of 3,462 cases and 6,125 controls suggested 789 mg/L as the Lp(a) cutoff value for discriminating individuals with CAD from those without CAD in the Chinese Han population (21). Another cross-sectional study proposed a level of Lp(a) <170 mg/L (after rounding, 80th percentile) as the cutoff value for identifying primary myocardial infarction in a Chinese health check-up population (23). Therefore, the cutoff value for Lp(a) is not written in stone and may vary depending on ethnicity and comorbidities. The addition of Lp(a) to CHD risk models has been shown to improve the net reclassification index (NRI) and C-statistic in previous studies of Caucasians (45).

Numerous clinical studies have indicated that increased

TC, LDL-C and TG and decreased HDL-C are risk factors for CHD (46-49). Few studies have explored whether the association between Lp(a) levels and the risk of CHD depends on the lipid profile. Our study indicated a positive association between Lp(a) levels and the risk of CHD in normolipidemic subgroups. However, this relationship was not detected in high-risk individuals with abnormal lipid profiles. In addition, our study indicated that elevated Lp(a) levels and dyslipidemia significantly contributed to a higher risk of CHD with synergistic effects. A synergistic effect was not found between Lp(a) and single abnormalities of TC, TG, HDL-C and LDL-C levels with regard to the risk for CHD. These findings suggest that the association between Lp(a) and CHD may be attenuated by receiving lipid-lowering medications among individuals at high risk of CHD (50). The prospective Cardiovascular Health Study revealed that increased Lp(a) levels were associated with a higher CVD risk, especially in those with LDL-C <70 mg/dL and those with higher healthcare costs (18). These studies strongly support the independent role of Lp(a) in mediating CVD events, which may explain the residual risk in patients on statin therapy (8). Our study suggests that the measurement of Lp(a) is necessary in normolipidemic patients, which would help identify those subjects at high risk of CHD.

Lipid-lowering drugs might be important confounders in the association of Lp(a) and CHD. Statins and niacin can significantly reduce serum TC, TG, LDL-C, and Apo B levels and mildly increase HDL-C levels (35). Fibrates target atherogenic dyslipidemia by increasing plasma HDL-C concentrations and decreasing small dense LDL (sdLDL) particle and TG levels (51). Ezetimibe is a cholesterol absorption inhibitor. A meta-analysis indicated that there was a significant 18.5% reduction in LDL-C

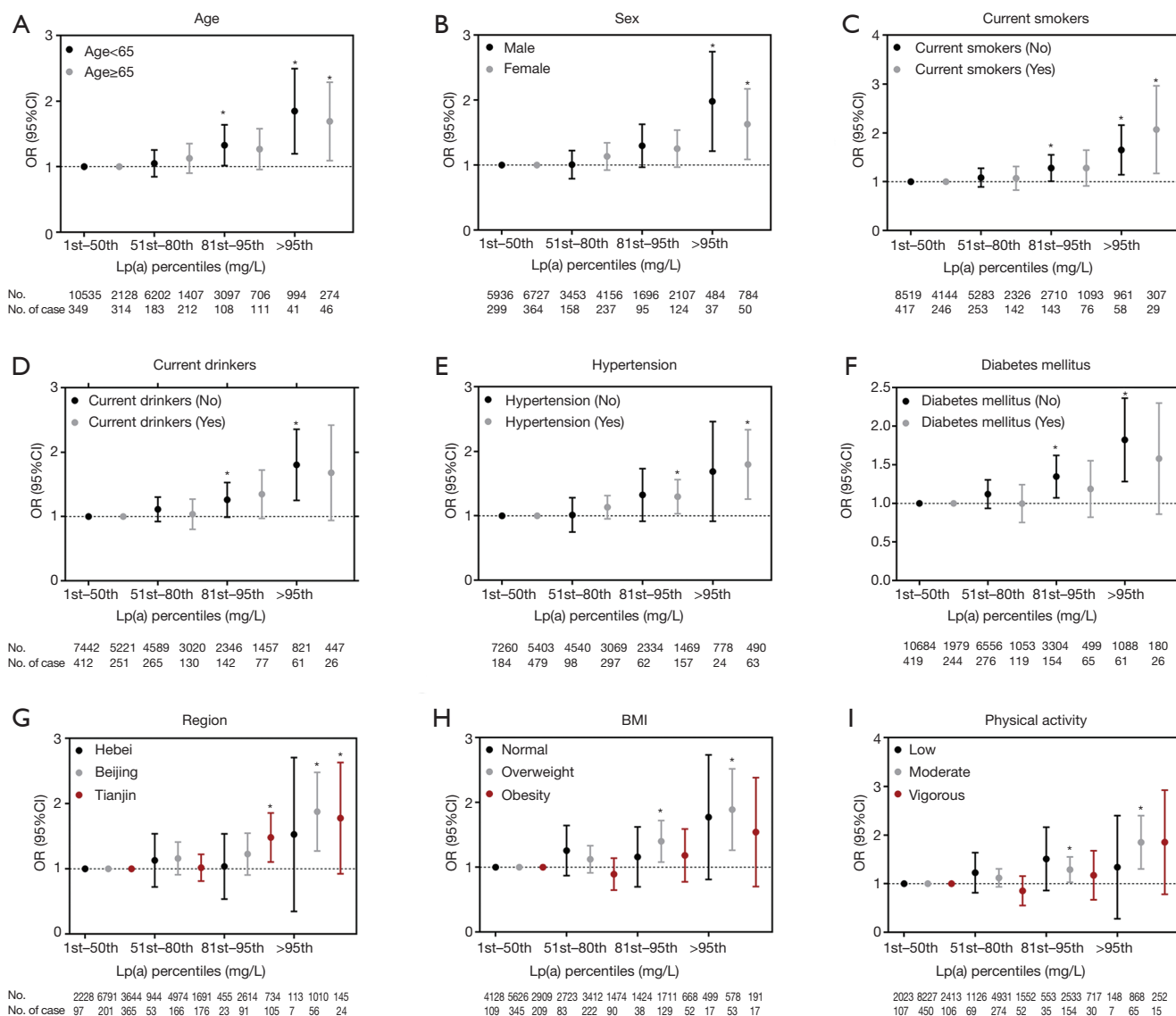


Figure 3 Odds ratios (95% CIs) for coronary heart disease in lipoprotein(a) percentiles stratified by age (A), sex (B), current smokers (C), current drinkers (D), hypertension (E), diabetes mellitus (F), region (G), BMI (H), and physical activity (I). * indicates $P < 0.05$. The model was adjusted for region, age, sex, BMI, TG, HDL-C, LDL-C, hsCRP, current smokers, current drinkers, physical activity, family history of CHD, hypertension, and diabetes mellitus (no adjustments were made for the variable for corresponding population stratification). CHD, coronary heart disease; Lp(a), lipoprotein(a); BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

level, 3% increase in HDL-C level, 8% reduction in TG level, and 13% reduction in TC level with ezetimibe compared with the placebo (52).

However, the effects of therapeutic agents on circulating levels of Lp(a) are not well understood (7). Several studies have shown that statins and ezetimibe actually increase Lp(a) levels, a seeming paradox because it is associated with

a cardiovascular benefit (53,54). A meta-analysis suggested that fibrates have a significantly greater effect with regard to reducing plasma Lp(a) concentrations than do statins (55).

There are currently no approved pharmacologic therapies that specifically target Lp(a). Niacin at doses ranging from 1–3 g per day has been shown to reduce Lp(a) levels by approximately 30% (56). However, niacin has

been shown to have poor tolerability and the potential for adverse effects. Mipomersen is an antisense oligonucleotide targeting apoB, thereby reducing the circulating levels of all apoB-containing lipoproteins. Mipomersen has been shown to lower Lp(a) levels by 20–50% (57). A randomized, double-blind, placebo-controlled, dose-ranging trial indicated that hepatocyte-directed antisense oligonucleotide AKCEA-APO(a)-LRx (APO(a)-LRx) reduced Lp(a) levels in a dose-dependent manner in patients who had elevated Lp(a) levels and established CVD (58). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, including evolocumab and alirocumab, have led to modest reductions in Lp(a) and LDL-C, with the most benefit seen in patients with higher absolute values (59,60). Lipoprotein apheresis is a very efficient method of lowering the levels of LDL-C, Lp(a) and other apoB containing lipoproteins, including triglyceride-rich lipoproteins (61). Moderate- and low-intensity statins remain the first-line treatment chosen in clinical practice in China. A combination of lipid-regulating drugs (ezetimibe, fenofibrate or PCSK9 inhibitors) may be considered for patients with statin intolerance, substandard cholesterol levels or severe combined hyperlipidemia (35).

To our knowledge, this is the largest sample size study to explore the association between Lp(a) and CHD in the general Chinese community population. The large sample size of the population in our study provided adequate statistical power to detect a positive association. Moreover, the use of standardized questionnaires, the same equipment and stringent, consistent criteria for measurements enabled the comparison of results across different subgroups of populations. Furthermore, the serum Lp(a) assay used is the one most widely accepted in research and clinical settings and is comparatively less labor intensive and expensive than other assays. Some limitations of this study also warrant discussion. This was a cross-sectional study and could not be used to determine any causal associations between elevated Lp(a) and an increased risk of CHD. Although the characteristics of the total population and the study participants included in the present study were significantly different, they were close numerically. This study was conducted only in the Chinese Han population, and therefore the results may not be representative of the situation in other ethnic groups in China. Moreover, we did not collect information about the use of lipid-lowering drugs, which would attenuate the strength of the association to some extent.

Conclusions

Our study found a linear and positive relationship between Lp(a) concentrations and the risk of CHD in the general Chinese community population, and the same association was found in the subgroups of normolipidemic subjects. Both dyslipidemia and elevated Lp(a) independently and synergistically contributed to the risk of CHD. More attention should be paid to the level of Lp(a) in normolipidemic subjects, as it may be an early predictor of the occurrence of CHD. Our results provide evidence that facilitates a better understanding of the role of Lp(a) levels and lipid profiles in CHD in the general Chinese community population.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3899>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Boards of Hebei Provincial Center for Disease Prevention and Control (No. IRB2017-003), Chaoyang

District Center for Disease Prevention and Control (No. CYCDPCIRB-20170830-1) and Capital Medical University (No. 2018SY81) and informed consent was obtained from all the patients.

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Table S1 Characteristics of participants in the present study participants and the total cohort population

Variables	Total cohort (n=33,391)	Study participants (n=25,343)
Age (years) *	50.11±14.35	50.69±14.44
Sex [male, (n, %)] *	14,853 (44.48)	11,569 (45.65)
BMI (kg/m ²) *	25.27±3.59	25.33±3.57
SBP (mmHg) *	129.36±18.93	130.23±19.06
DBP (mmHg)	77.68±11.65	77.58±11.70
Fasting glucose (mmol/L) *	5.40 (5.00,5.91)	5.46 (5.04,6.00)
hsCRP (mg/L)	1.06 (0.65,1.74)	1.06 (0.53,2.17)
TC≥6.2 mmol/L*	4,285(12.83)	3,636(14.35)
TG≥2.3 mmol/L	5,683(17.02)	4,312(17.01)
HDL-C<1.0 mmol/L*	4,795(14.36)	3,465(13.67)
LDL-C≥4.1 mmol/L*	3,113(9.32)	2,672(10.54)
Lp(a)≥300 mg/L (n, %)	4,761(18.28)	4,617 (18.22)
Region (n, %) *		
Hebei	10,427 (31.23)	3,740 (14.76)
Beijing	16,166 (48.41)	15,389 (60.72)
Tianjin	6,798 (20.36)	6,214 (24.52)
Current smokers (n, %)	10,278 (30.78)	7,870 (31.05)
Current drinkers (n, %) *	14,156 (42.39)	10,145 (40.03)
Physical activity (n, %) *		
Low	5,512 (16.51)	3,850 (15.19)
Moderate	21,837 (65.40)	16,559 (65.34)
Vigorous	6,042 (18.09)	4,934 (19.47)
CHD (n, %) *	2,241(6.71)	1,364(5.38)
Family history of CHD (n, %) *	7,132 (21.36)	4,854 (19.15)
Hypertension (n, %)	13,524 (40.50)	10,431 (41.16)
Diabetes mellitus (n, %) *	4,618 (13.83)	3,711 (14.64)

*P<0.05. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); CHD, coronary heart disease.

Table S2 Percentiles and corresponding levels of lipoprotein(a) in the total population

Variables	Lp(a) percentiles					
	25	50	75	80	85	95
Lp(a) (mg/L)	59.0	119.0	236.7	281.2	342.7	607.9

Abbreviations: Lp(a), lipoprotein(a).

Table S3 Characteristics of participants according to dichotomous Lp(a) levels

Variables	Total	Lp(a) levels (mg/L)		P
		<300	≥300	
Age (years)	50.69±14.44	50.58±14.32	51.18±14.96	0.0128
Sex [male, (n, %)]	11,569(45.65)	9,607(46.35)	1,962(42.50)	<0.0001
BMI (kg/m ²)	25.33±3.57	25.41±3.59	25.01±3.46	<0.0001
SBP (mmHg)	130.23±19.06	130.59±19.08	128.61±18.85	<0.0001
DBP (mmHg)	77.58±11.70	77.83±11.71	76.45±11.57	<0.0001
Fasting glucose (mmol/L)	5.46(5.04,6.00)	5.43(5.00,6.00)	5.50(5.10,6.00)	<0.0001 [†]
hsCRP (mg/L)	1.06(0.53,2.17)	1.06(0.52,2.16)	1.06(0.55,2.23)	0.1280 [†]
Lp(a) (mg/L)	119.0(59.0,236.7)	94.2(50.3,160.0)	457.7(362.6,628.1)	<0.0001 [†]
TC≥6.2 mmol/L	3,636(14.35)	2,738(13.21)	898(19.45)	<0.0001
TG≥2.3 mmol/L	4,312(17.01)	3,713(17.91)	599(12.97)	<0.0001
HDL-C<1.0 mmol/L	3,465(13.67)	3,026(14.60)	439(9.51)	<0.0001
LDL-C≥4.1 mmol/L	2,672(10.54)	1,997(9.64)	675(14.62)	<0.0001
Region (n, %)				<0.0001
Hebei	3,740(14.76)	3,223(15.55)	517(11.20)	
Beijing	15,389(60.72)	12,083(58.30)	3,306(71.60)	
Tianjin	6,214(24.52)	5,420(26.15)	794(17.20)	
Current smokers (n, %)	7,870(31.05)	6,614(31.91)	1,256(27.20)	<0.0001
Current drinkers (n, %)	10,145(40.03)	8,417(40.61)	1,728(37.43)	<0.0001
Physical activity (n, %)				0.0053
Low	3,850(15.19)	3,212(15.50)	638(13.82)	
Moderate	16,559(65.34)	13,458(64.93)	3,101(67.16)	
Vigorous	4,934(19.47)	4,056(19.57)	878(19.02)	
Family history of CHD (n, %)	4,854(19.15)	3,926(18.94)	928(20.10)	0.0707
CHD (n, %)	1364(5.38)	1,079(5.21)	285(6.17)	0.0085
Hypertension (n, %)	10,431(41.16)	8,656(41.76)	1,775(38.44)	<0.0001
Diabetes mellitus (n, %)	3,711(14.64)	3,088(14.90)	623(13.49)	0.0146

Notes. [†]Wilcoxon rank-sum test. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); CHD, coronary heart disease.

Table S4 Univariate analysis of dichotomous lipoprotein(a) and lipid profiles in the total population

Lipid profiles	Lp(a) (mg/L)		P
	<300	≥300	
TC (mmol/L)			<0.0001
<6.2	17,988(82.87)	3,719(17.13)	
≥6.2	2,738(75.30)	898(24.70)	
TG (mmol/L)			<0.0001
<2.3	17,013(80.89)	4,018(19.11)	
≥2.3	3,713(86.11)	599(13.89)	
HDL-C (mmol/L)			<0.0001
≥1.0	17,700(80.90)	4,178(19.10)	
<1.0	3,026(87.33)	439(12.67)	
LDL-C (mmol/L)			<0.0001
<4.1	18,729(82.61)	3,942(17.39)	
≥4.1	1,997(74.74)	675(25.26)	
Dyslipidemia (n, %)			0.1724
No	12,199(82.06)	2,667(17.94)	
Yes	8,527(81.39)	1,950(18.61)	
Type of dyslipidemia (n, %)			0.0117
Normolipidemia	13,516(81.66)	3,036(18.34)	
One abnormality	3,701(83.15)	750(16.85)	
Two abnormalities	2,844(81.33)	653(18.67)	
≥Three abnormalities	665(78.88)	178(21.12)	

Abbreviations: Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table S5 Univariate analysis of lipoprotein(a) percentiles and lipid profiles in the total population

Lipid profiles	Lp(a) percentiles (mg/L)				P
	<50th (<119.0)	51st-80th (119.0-281.2)	81st-95th (281.2-607.9)	>95th (>607.9)	
TC (mmol/L)					<0.0001
<6.2	11,190(51.55)	6,422(29.58)	3,115(14.35)	980(4.51)	
≥6.2	1,473(40.51)	1,187(32.65)	688(18.92)	288(7.92)	
TG (mmol/L)					<0.0001
<2.3	10,051(47.79)	6,558(31.18)	3,321(15.79)	1,101(5.24)	
≥2.3	2,612(60.58)	1,051(24.37)	482(11.18)	167(3.87)	
HDL-C (mmol/L)					<0.0001
≥1.0	10,562(48.28)	6,737 (30.79)	3,418(15.62)	1,161(5.31)	
<1.0	2,101(60.63)	872(25.17)	385(11.11)	107(3.09)	
LDL-C (mmol/L)					<0.0001
<4.1	11,650(51.39)	6,682(29.47)	3,300(14.56)	1,039(4.58)	
≥4.1	1,013(37.91)	927(34.69)	503(18.82)	229(8.57)	
Dyslipidemia (n, %)					0.7622
No	7,322(49.25)	4,598(30.93)	2,256(15.18)	690(4.64)	
Yes	5,341(50.98)	3,011(28.74)	1,547(14.77)	578(5.52)	
Type of dyslipidemia (n, %)					<0.0001
Normolipidemia	8,083(48.83)	5,128(30.98)	2,532(15.30)	809(4.89)	
One abnormality	2,422(54.41)	1,203(27.03)	635(14.27)	191(4.29)	
Two abnormalities	1,749(50.01)	1,039(29.63)	504(14.41)	208(5.95)	
≥Three abnormalities	409(48.52)	242(28.71)	132(15.66)	60(7.12)	

Abbreviations: Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table S6 Associations of dichotomous lipoprotein(a) with coronary heart disease according to different lipid profiles

Population	CHD (n, %)	Univariate [†]	Multivariate ^{†‡}
Total	1,364 (5.38)	1.20 (1.05, 1.37)	1.36 (1.17, 1.57)
Normolipidemia	557 (3.75)	1.23 (1.00, 1.51)	1.41 (1.12, 1.77)
Dyslipidemia	807 (7.70)	1.16 (0.97, 1.39)	1.24 (1.02, 1.50)
Type of dyslipidemia			
Normolipidemia	832 (5.03)	1.28 (1.08, 1.52)	1.42 (1.18, 1.70)
One abnormality	267 (6.00)	1.12 (0.81, 1.54)	1.22 (0.86, 1.73)
Two abnormalities	199 (5.69)	0.99 (0.69, 1.44)	1.05 (0.71, 1.54)
≥Three abnormalities	66 (7.83)	1.11 (0.61, 2.02)	1.48(0.75, 2.92)
TC<6.2 mmol/L	1,158 (5.33)	1.23 (1.06, 1.42)	1.38 (1.17, 1.62)
TC≥6.2 mmol/L	206 (5.67)	1.06 (0.77,1.46)	1.33 (0.94, 1.89)
TG<2.3 mmol/L	1,091 (5.19)	1.23 (1.07, 1.43)	1.39 (1.18, 1.63)
TG≥2.3 mmol/L	273 (6.33)	1.10 (0.78,1.56)	1.23 (0.85, 1.79)
HDL-C≥1.0 mmol/L	1,140 (5.21)	1.25 (1.08, 1.44)	1.38 (1.18, 1.62)
HDL-C<1.0 mmol/L	224 (6.46)	0.98 (0.65, 1.48)	1.18 (0.75, 1.84)
LDL-C<4.1 mmol/L	1,198 (5.28)	1.19 (1.03, 1.38)	1.35 (1.15, 1.59)
LDL-C≥4.1 mmol/L	166 (6.21)	1.18 (0.83, 1.68)	1.43 (0.98, 2.10)

Notes: [†] Compared with Lp(a)<300 mg/L. [‡] Adjusted for region, age, sex, BMI, TG, HDL-C, LDL-C, hsCRP, current smokers, current drinkers, physical activity, family history of CHD, hypertension, diabetes mellitus. Abbreviations: CHD, coronary heart disease; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein.

Table S7 Associations of lipoprotein(a) percentiles with coronary heart disease according to different lipid profiles

Lipid profile and Lp(a) percentiles	CHD (n, %)	OR (95%CI)
Dyslipidemia & Lp(a)		
Dyslipidemia (-) & Lp(a) (<50th)	264(3.61)	1.00
Dyslipidemia (-) & Lp(a) (51st-80th)	166(3.61)	1.06 (0.86, 1.31)
Dyslipidemia (-) & Lp(a) (81st-95th)	90(3.99)	1.25 (0.96, 1.62)
Dyslipidemia (-) & Lp(a) (>95th)	37(5.36)	2.07 (1.41, 3.03)
Dyslipidemia (+) & Lp(a) (<50th)	399(7.47)	1.40 (1.18, 1.67)
Dyslipidemia (+) & Lp(a) (51st-80th)	229(7.61)	1.46 (1.20, 1.77)
Dyslipidemia (+) & Lp(a) (81st-95th)	129(8.34)	1.68 (1.33, 2.12)
Dyslipidemia (+) & Lp(a) (>95th)	50(8.65)	1.81 (1.29, 2.54)
TC & Lp(a)		
TC (-) & Lp(a) (<50th)	578(5.17)	1.00
TC (-) & Lp(a) (51st-80th)	330(5.14)	1.09 (0.94, 1.27)
TC (-) & Lp(a) (81st-95th)	175(5.62)	1.24 (1.02, 1.50)
TC (-) & Lp(a) (>95th)	75(7.65)	1.96 (1.49, 2.59)
TC (+) & Lp(a) (<50th)	85(5.77)	0.73 (0.54, 0.99)
TC (+) & Lp(a) (51st-80th)	65(5.48)	0.74 (0.53, 1.03)
TC (+) & Lp(a) (81st-95th)	44(6.40)	1.03 (0.71, 1.51)
TC (+) & Lp(a) (>95th)	12(4.17)	0.65 (0.34, 1.25)
TG & Lp(a)		
TG (-) & Lp(a) (<50th)	506(5.03)	1.00
TG (-) & Lp(a) (51st-80th)	324(4.94)	1.03 (0.88, 1.20)
TG (-) & Lp(a) (81st-95th)	185(5.57)	1.24 (1.02, 1.49)
TG (-) & Lp(a) (>95th)	76(6.90)	1.66 (1.27, 2.19)
TG (+) & Lp(a) (<50th)	157(6.01)	0.96 (0.79, 1.18)
TG (+) & Lp(a) (51st-80th)	71(6.76)	1.24 (0.94, 1.65)
TG (+) & Lp(a) (81st-95th)	34(7.05)	1.33 (0.90, 1.96)
TG (+) & Lp(a) (>95th)	11(6.59)	1.64 (0.85, 3.16)
HDL-C & Lp(a)		
HDL-C (-) & Lp(a) (<50th)	522(4.94)	1.00
HDL-C (-) & Lp(a) (51st-80th)	345(5.12)	1.08 (0.93, 1.26)
HDL-C (-) & Lp(a) (81st-95th)	193(5.65)	1.27 (1.06, 1.53)
HDL-C (-) & Lp(a) (>95th)	80(6.89)	1.75 (1.34, 2.28)
HDL-C (+) & Lp(a) (<50th)	141(6.71)	1.25 (1.01, 1.56)
HDL-C (+) & Lp(a) (51st-80th)	50(5.73)	1.26 (0.91, 1.75)
HDL-C (+) & Lp(a) (81st-95th)	26(6.75)	1.56 (0.99, 2.44)
HDL-C (+) & Lp(a) (>95th)	7(6.54)	1.44 (0.62, 3.34)
LDL-C & Lp(a)		
LDL-C (-) & Lp(a) (<50th)	594(5.10)	1.00
LDL-C (-) & Lp(a) (51st-80th)	345(5.16)	1.09 (0.94, 1.27)
LDL-C (-) & Lp(a) (81st-95th)	183(5.55)	1.24 (1.03, 1.50)
LDL-C (-) & Lp(a) (>95th)	76(7.31)	1.93 (1.47, 2.53)
LDL-C (+) & Lp(a) (<50th)	69(6.81)	0.82 (0.63, 1.09)
LDL-C (+) & Lp(a) (51st-80th)	50(5.39)	0.76 (0.56, 1.04)
LDL-C (+) & Lp(a) (81st-95th)	36(7.16)	1.10 (0.76, 1.60)
LDL-C (+) & Lp(a) (>95th)	11(4.80)	0.69 (0.36, 1.31)

Dyslipidemia (-): without dyslipidemia; Dyslipidemia (+): with dyslipidemia. TC (-): TC<6.2 mmol/L; TC (+): TC≥6.2 mmol/L. TG (-): TG<2.3 mmol/L; TG (+): TG≥2.3 mmol/L. HDL-C (-): HDL-C≥1.0 mmol/L; HDL-C (+): HDL-C<1.0 mmol/L. LDL-C (-): LDL-C<4.1 mmol/L; LDL-C (+): LDL-C≥4.1 mmol/L. Lp(a) (<50th): <119.0 mg/L; Lp(a) (51st-80th): (119.0-281.2) mg/L; Lp(a) (81st-95th): (281.2-607.9) mg/L; Lp(a) (>95th): >607.9 mg/L. Abbreviations: CHD, coronary heart disease; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

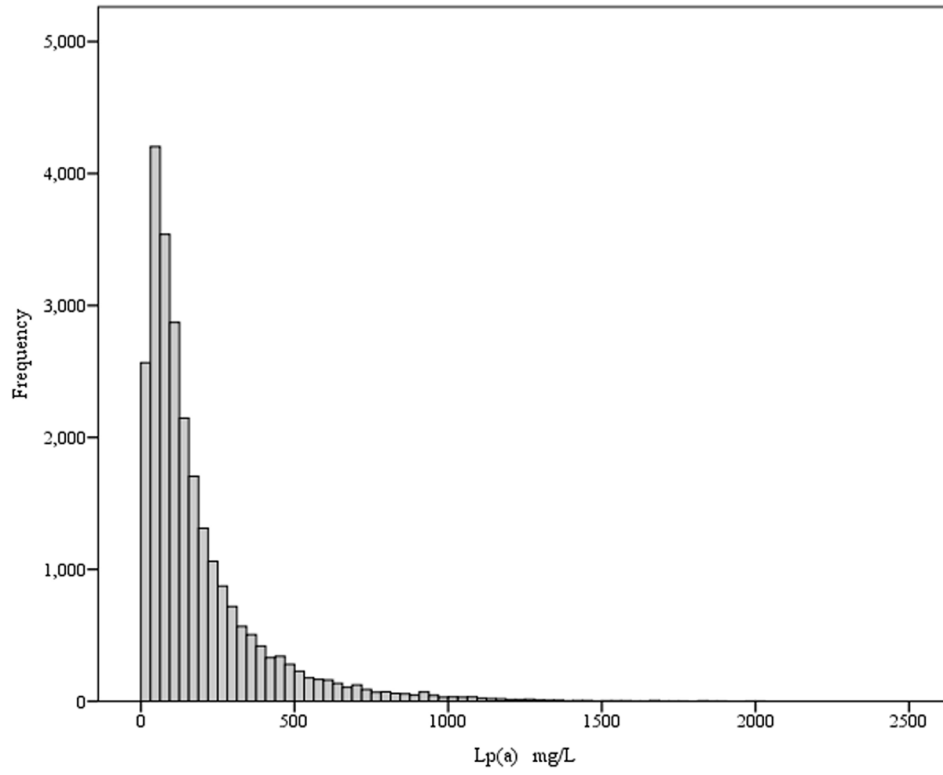


Figure S1 Distribution of serum lipoprotein(a) levels in the total population. Lp(a), lipoprotein(a).